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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

CONTINUATION SHEET

The amendment filed 4/13/2009 under 37 CFR 1.116 in reply to the final rejection has NOT been entered, because it is not in compliance with 37 CFR 1.121. See the attached Notice of Non-Compliant Amendment. The final Office action, mailed 1/5/2009, is maintained.

With regard to Applicant's arguments directed to the claim objections and rejections under 35 U.S.C. 112, second paragraph, all arguments are directed to the newly amended claims. As discussed above, the amendments have not been entered. Therefore, the arguments are moot and will not be addressed.

With respect to the rejection of claims 1-4, 6, 11, 12 and 14-25 under 35 U.S.C. 112, first paragraph, Applicant's arguments filed 4/13/2009 have been fully considered but they are not persuasive.

The response asserts that the specification teaches that based upon the expression of at least one gene selected from MNSOD genes, TXNRD1 genes and GPX1 genes, the sensitivity of correctly classifying a tumor patient as a subject having a tumor is 87, 67 and 62%, respectively. The specification points to the working example at pages 46 and 47 of the instant specification. The response notes that almost 100 patients with various tumor types were included in the study. Further, the response asserts that it flows logically that the sensitivity will be higher if expression of at least two genes is determined. Moreover, the response asserts that the working example corroborates that the method of the present invention enables the diagnosis of a tumor.

The Examiner discusses the working example at pages 12-14 of the Office action mailed 1/5/2009. The working example represents an enabled embodiment that falls within the scope of what is claimed. The Examiner has indicated the enablement of that particular embodiment in

the scope of enablement rejection of record. However, the claims are much broader in scope than the working example, and it would be unpredictable to extrapolate the results of the working example to the full scope of the claimed invention (see the discussion at pages 2-3 of the specification and pages 15-18 of the Office action mailed 1/5/2009).

The response traverses the Examiner's assertion that the data described in the Declaration of Professor Giesing is not commensurate in scope with the claimed invention. The response asserts that the selection of individuals based upon a PSA level between 4 to 10 ng/ml is not required to enable the claimed invention.

These arguments are not found persuasive. The data presented in the declaration is not commensurate in scope with the claims regardless of whether selection of individuals based upon PSA levels between 4 to 10 ng/ml is required to enable the claimed invention. The first step of the independent claim is "obtaining a cell-containing fraction from the body fluid with enrichment of cancer cells and determining in the cell-containing fraction the expression of at least 2 genes which are selected from the group consisting of i) manganese superoxide dismutase genes; ii) thioredoxin reductase 1 genes; and iii) glutathione peroxidase 1 genes...wherein the body fluid is selected from blood and bone marrow." The specification defines the term "manganese superoxide dismutase (MNSOD)" to mean enzymes which catalyze the decomposition of superoxide free radicals to form hydrogen peroxide, and in particular the enzymes which constitute enzyme class 1.15.1.1 (paragraph bridging pages 14-15). The enzymes of this class are not limited to manganese-containing superoxide dismutase enzymes (see page 9 of the Office action mailed 1/5/2009). The declaration uses primers that are identical to SEQ ID NOs: 1 and 2 of the present specification to amplify the human SOD2 gene from

chromosome 6q25. The expression of other enzymes of enzyme class 1.15.1.1 is not tested in the declaration. Further, the declaration measures TXNRD1 from human chromosome 12q23-q24.1 with primers identical to SEQ ID NOs: 4 and 5 of the present specification, and the declaration measures GPX1 from human chromosome 3p21.3 with primers identical to SEQ ID NOs: 7 and 8 of the specification. The declaration notes the specific transcript variants that may be detected with the specific primer used. However, the claims encompass the use of different primers or the use of antibodies to the proteins, which may result in other variants being measured. All measurements were made using cells isolated from human peripheral blood. The only method to provide for "enrichment of cancer cells" was filtration over a 20 μm mesh. Thus, the declaration does not provide enablement for any species of organisms, or the use of any sample from any source of body fluid or tissue as a comparable biological sample. The method disclosed in the declaration appears to be essentially the same method disclosed in the working example and detailed in the scope of enablement rejection, except that selection of CD45 positive cells does not appear to have been performed. Given the unpredictability of the invention (see pages 2-3 of the specification and pages 15-18 of the Office action mailed 1/5/2009), it would be unpredictable for one to extrapolate the results obtained in the working example to the full scope of the claimed invention.

The response notes that the Declaration showed that distant relapse of prostate cancer was predicted with GPX1 and SOD2, and local relapse of prostate cancer was predicted with GPX1, SOD2 and TXNRD1. The response asserts that this data enables estimating the risk to develop metastasis or recurrence of any type of cancer. Further, the response notes that there is no claim directed to differentiating local from distant relapse. The response notes that the

specification teaches the combination of an MNSOD gene with a GPX1 gene as well as the combination of an MNSOD gene, GPX1 gene, and TXNRD1 gene. The response asserts that it would be within the skill of the art to select particular gene combinations for addressing particular questions of diagnostic relevance. The response asserts that the working examples of the specification show that there was a clear correlation between the measured elevated expression of the MNSOD, TXNRD1 and GPX1 genes and the recurrences in the group of tumor patients tested.

These arguments are not found persuasive. The evidence presented in the declaration is not commensurate in scope with the claims, and it would have been unpredictable at the time the invention was made to extrapolate the results of the declaration to the prediction or estimation of the risk to develop a metastasis or a recurrence in any type of cancer using any of the claimed gene combinations. The claims encompass the use of MNSOD genes other than SOD2. The claims encompass combinations of two genes such as GPX1 and TXNRD1 or SOD 2 and TXNRD1, which are not enabled by the specification or declaration. There are no working examples where the measurement of gene expression or protein expression of the claimed genes is used to predict or estimate the risk to develop a metastasis or recurrence. All of the test subjects were known to have cancer, but there is no information with regard to the presence of metastasis or recurrence in the subjects. Given the variable expression of the enzymes based upon tumor or cell type and the expression of multiple different isoforms, it would be unpredictable to extrapolate the results of the declaration to any cancer type, any combination of any of the genes encompassed by the claims, any of body fluid or tissue for comparison, or any species of organism, for example.

The response asserts that one of skill in the art would distinguish between MNSOD and CuZnSOD, and the term "MNSOD" would not be understood to encompass both MNSOD and CuZnSOD. The response asks how the term "MNSOD" could be understood to encompass both MNSOD and CuZnSOD.

An applicant is entitled to be his or her own lexicographer and may rebut the presumption that claim terms are to be given their ordinary and customary meaning by clearly setting forth a definition of the term that is different from its ordinary and customary meaning(s). *See In re Paulsen*, 30 F.3d 1475, 1480, 31 USPQ2d 1671, 1674 (Fed. Cir. 1994). In the instant case, Applicant has acted as his own lexicographer to specifically define the term "manganese superoxide dismutase (MNSOD)" to encompass both MNSOD and CuZnSOD even though this would be contrary to the ordinary meaning of manganese superoxide dismutase (MNSOD). The written description clearly redefines the claim term and sets forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant has intended to so define the claim term "manganese superoxide dismutase." The definition is provided at page 14, lines 35-38:

> The term "manganese superoxide dismutase (MNSOD for short) according to the invention refers to enzymes which catalyze the decomposition of superoxide free radicals (O_2^-) to form hydrogen peroxide (H_2O_2). These

The specification goes on to state that the enzymes include the enzymes of enzyme class 1.15.1.1 (sentence bridging pages 14-15). The Examiner provided a printout of the entry for 1.15.1.1 from the Enzyme nomenclature databases, accessed from http://us.expasy.org/enzyme, in the Office action mailed 5/15/2008. This class includes all superoxide dismutase enzymes, including

iron, manganese, copper, and zinc superoxide dismutase. All of these enzymes catalyze the decomposition of superoxide free radicals to form hydrogen peroxide and thus fall within the scope of what is claimed based upon Applicant's own definition of the term "manganese superoxide dismutase (MNSOD)."

The response asserts that the Examiner has not provided reasoning or evidence that one skilled in the art could not practice the invention without undue experimentation. The response again asserts that the working example enables the claimed invention. The response notes that the working example shows that a wide variety of cancers express the genes in a manner which enables the detection of disseminated cancer cells. Further, the response asserts that it does not matter which isoform of the gene is expressed.

It is noted that the Examiner has put forth a scope of enablement rejection directed to the enabled scope provided by the working example. The enabled scope is not limited to a particular type of cancer. However, the specification does teach that it is particularly important to determine whether expression in the cells of the investigated sample is comparatively elevated (e.g., page 28, lines 1-10). As written, the claims encompass a comparison to any "further cell-containing fraction of the body fluid" or any "comparable biological sample," which may be any body fluid or solid tissue from any source. The step of comparing is critical to the outcome of the invention, and it must be determined experimentally whether any type of comparison will provide a reliable indicator of the presence of a tumor or the risk of metastasis or recurrence. The Examiner has set forth evidence of the unpredictability of the invention at pages 15-18 of the prior action. Given the breadth of the claims, and the unpredictability in extrapolating the results disclosed in the working example to the full scope of the claimed invention, it would require a

large amount of unpredictable experimentation to practice the full scope of the claimed invention to detect the presence of disseminated cancer cells, provide the diagnosis of a tumor, estimate the risk to develop a metastasis, and estimate the risk to develop a recurrence. Seven et al (Clinical Biochemistry, Vol. 32, No. 5, pages 369-373, 1999, of record) state the following at page 372:

> Several reports have found antioxidants and enzymes related to the antioxidant function at increased levels in serum, erythrocytes, or tumor tissue of early stage cancer patients when compared with controls (9,29). The high levels of antioxidants were suggested to be a self-serving feature developed by tumor cells, eventually providing a selective advantage for proliferation (29).
>
> In line with our findings, Gerber *et al.* (29) reported significant higher plasma vitamin E levels in breast cancer. In contrast with these studies, Palan *et al.* (5) reported decreased plasma levels of antioxidants in cervical cancer patients compared with normal subjects. Lower plasma vitamin C and E levels were observed in malign breast tumors compared with controls (21). The controversial findings in the literature related to lipid peroxidation and antioxidant status in cancer may arise from the type of cancer/tissue studied. The adaptive antioxidant response against oxidant stress is thought to be tissue specific. The constitutive levels and the inducibility of the antioxidant enzymes SOD, GSH Px, and catalase vary for different tissues.
>
> Oxidation system along with its components is complex and the inconsistency of the data from the literature is possibly because of different cancer types, cancer grades, or other characteristics of the patients examined.

Thus, Seven et al provide evidence of the unpredictable nature of the invention. One skilled in the art could not readily anticipate the effect of a change in the subject matter with regard to the different uses of the method or with regard to varying the method steps from those specifically disclosed in the specification. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Thus, specific guidance is what is needed rather than general guidance (e.g., a statement than any

comparison could be used). The Examiner has set forth a *prima facie* case of lack of enablement, and the evidence on the record as a whole is not sufficient to overcome the rejection.

The response asserts that the claimed invention does not encompass erythrocytes, because erythrocytes don't have genes. This argument is not found persuasive, because the claims are not directed to directly measuring the copy number of a gene *per se*. The claims are directed to measuring the expression of genes. For example, gene expression products include mRNA and protein, for example. The claims read on detecting the level of protein expression of the claimed genes. Clearly, erythrocytes contain proteins, because Seven et al (1999) teach that CuZn SOD and glutathione peroxidase were not increased in the red blood cell fraction of laryngeal cancer patients (e.g., page 372, paragraph bridging columns; Table 1).

The response asserts that it does not require undue experimentation to identify specific comparisons, because the type of experimentation required is routine in the art. Further, the response asserts that a comparison is not required at all. The response states, "The inventors believe that said antioxidant overexpression in disseminated cancer cells can be described as a survival and defense mechanism required in an atypical environment. It is therefore the fundamental principle of the method of the present invention to determine whether the cells in a fraction obtained from the body fluid with enrichment of cancer cells overexpress the genes at stake."

These arguments are not found persuasive, because the evidence on the record indicates that the fundamental principle of the method is not sufficient to fully enable the claimed invention. Seven et al (Clinical Biochemistry, Vol. 32, No. 5, pages 369-373, 1999, of record) state the following at page 372:

> Several reports have found antioxidants and enzymes related to the antioxidant function at increased levels in serum, erythrocytes, or tumor tissue of early stage cancer patients when compared with controls (9,29). **The high levels of antioxidants were suggested to be a self-serving feature developed by tumor cells, eventually providing a selective advantage for proliferation (29).**
>
> In line with our findings, Gerber *et al.* (29) reported significant higher plasma vitamin E levels in breast cancer. In contrast with these studies, Palan *et al.* (5) reported decreased plasma levels of antioxidants in cervical cancer patients compared with normal subjects. Lower plasma vitamin C and E levels were observed in malign breast tumors compared with controls (21). **The controversial findings in the literature related to lipid peroxidation and antioxidant status in cancer may arise from the type of cancer/tissue studied. The adaptive antioxidant response against oxidant stress is thought to be tissue specific. The constitutive levels and the inducibility of the antioxidant enzymes SOD, GSH Px, and catalase vary for different tissues.**
>
> **Oxidation system along with its components is complex and the inconsistency of the data from the literature is possibly because of different cancer types, cancer grades, or other characteristics of the patients examined**. (Emphasis added)

Thus, Seven et al provide evidence of the unpredictable nature of the invention. While the working example of the present specification appears to be enabled, it would require a large amount of experimentation to extrapolate those results to other methods of comparison.

The response notes that standardization of expression to a housekeeping gene is standard and well-known to a person skilled in the art. The Examiner agrees with this statement.

The response asserts that it is clear that the nature of the comparative cell does not affect the expression value determined on the cancer cell fraction. The response asserts that only the ratio between the expression value of the cancer cells and the comparative cells may change depending on the kind of cancer cell used. The response notes that the method needs to be validated on a number of patients in clinical settings, as reflected by the data presented in Professor Giesing's declaration. However, the response asserts that such a validation is not

required to enable the method. The response notes that FDA approval is not required for a patent specification to be enabling.

If the ratio between the expression value of the cancer cells and the comparative cells changes, then it may not reliably predict the presence of disseminated tumor cells or allow for the diagnosis of a tumor, etc. The method relies upon an increase in expression of the claimed genes in the disseminated cancer cells. If the comparative tissue contains higher levels of expression, then it may be determined that cancer cells are not present when in fact they are. The Examiner is not taking into account any standards that the FDA may have. It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. In instant case diagnosing a tumor, predicting the risk of cancer metastasis, and predicting the risk of cancer recurrence by gene expression analysis is not considered routine in the art and without sufficient guidance to a specific process to achieve the full scope of the claimed outcomes the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement

made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and the amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the full scope of the invention as claimed.

The response asserts that the Examiner is requiring full predictive and prognostic data for every tumor entity.

This statement is not accurate. The Examiner has set forth a scope of enablement rejection that is not limited to any particular tumor type. The enabled scope is directed to the detection of disseminated cancer cells from any cancer type.

The response asserts that the data presented in the declaration of Professor Giesing exceeds by far the data that are usually seen in patent applications.

This is not found persuasive because each case must be evaluated on the merits presented therein. Upon evaluation of the instant specification and evidence on the record, the disclosure is not enabling for the reasons set forth above.

The response asserts that the data submitted may reach FDA approval based upon the probability of relapse free survival over time. As noted above, this data is not commensurate in scope with the claims.

The response notes that given the dynamics of disseminated cancer cells in a patient's tumor life, the compartment which is nearest to blood is bone marrow. The response notes that bone marrow sampling is invasive and not readily available but has been used in diagnostics. The response provides a post-filing review article published in 2006 that focuses on breast

cancer. The response asserts that the history of tumor cell findings in the bone marrow of breast cancer patients indicates that the claimed method can be applied to bone marrow.

These arguments are not persuasive. While tumor cells might be present in bone marrow, it is not clear that comparing the expression level of any two genes selected from manganese superoxide dismutase genes, thioredoxin reductase genes, and glutathione reductase genes in bone marrow to the expression in a different body fluid of the subject (e.g., blood, which may also have cancer cells) or any "comparable" sample would result in the claimed outcome.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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